

REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-17 are pending. The limitation of original claim 3 is incorporated into the independent claim. Claim 3 as amended is directed to stable transfectants. The subject of original claim 5 is split into amended claims 5 and 7. Other amendments of the claims are directed to correcting informalities that by their nature (e.g., misspelling and punctuation errors) clarify and do not limit the originally intended scope of protection.

New claims 8-10 are supported by page 6, lines 5-21, of the specification. New claims 11-18 are directed to a DNA construct comprised of a gene encoding a protein of interest operably linked to a heat-inducible promoter, the DNA construct is stably transfected into an immortalized human hepatocyte cell line, and expression of the protein of interest in that stably transfected and immortalized cell line is induced by increasing the temperature.

Claim/Specification Objections

Claims 1-3 and the specification were objected to by the Examiner as allegedly informal. They are corrected as suggested by her on pages 2-3 of the Action.

Withdrawal of the objections is requested.

35 U.S.C. 112 – Definiteness

Claims 1-6 were rejected under Section 112, second paragraph, as being allegedly “indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.” Applicant traverses as the term “normal” (i.e., a growth temperature) is deleted from claim 1 because this limitation is not required for patentability.

Applicant requests withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 1-2 were rejected under Section 102(b) as allegedly anticipated by Tsang et al. (U.S. Patent Publication No. 2003/0207832). Applicant traverses because the limitation of claim 3 is incorporated into the independent claim.

Applicant's invention derives from his combination of a modified heat-inducible promoter to transcribe a gene in a DNA construct and the latter's transformation or transfection into a human hepatocyte cell line. Most recombinant proteins are produced in Chinese hamster ovary (CHO) cell lines. But since they are produced in a non-human cell line, the recombinant proteins may be inappropriately post-translationally modified. This can lead to reduced biological activity of the recombinant protein or an immune response against it because it differs from native protein. Applicant selected human hepatocyte cell lines over other types of human cell lines (e.g., HEK293 or PER.C6 are discussed on pages 15-16 of the specification) that were available at the time he made the invention. Applicant's invention will provide higher yield for protein production than use of the same DNA construct transformed or transfected into a CHO cell line. Tsang et al. only disclose transfection of either MCF-7, a human breast carcinoma cell line, or SW480, a human colon carcinoma cell line.

Therefore, the cited document does not anticipate the claimed invention because it does not disclose all limitations of independent claim 1. Moreover, claim 2 depending from the independent claim is also not anticipated by the document because the limitations of claim 1 are incorporated in claims depending therefrom. See *In re McCarn*, 101 USPQ 411, 413 (C.C.P.A. 1954).

Withdrawal of the Section 102 rejection is requested because all limitations of the claimed invention are not disclosed by the cited document.

35 U.S.C. 103 – Nonobviousness

To establish a case of prima facie obviousness, all of the claim limitations must be taught or suggested by the prior art. See M.P.E.P. § 2143.03. Obviousness can only be established by combining or modifying the prior art teachings to produce the claimed invention if there is some teaching, suggestion, or motivation to do so found in either the references themselves or in the knowledge generally available to a person of ordinary skill in the art. See, e.g., *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); *In re Jones*, 21 USPQ2d 1941, 1943-44 (Fed. Cir. 1992). Evidence of the teaching, suggestion or motivation to combine or to modify references may come explicitly from statements in the prior art, the knowledge of a person of ordinary skill in the art or the nature of the problem to be solved, or may be implicit from the prior art as a whole rather than expressly stated in a reference. See *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999); *In re Kotzab*, 55 USPQ2d 1313, 1316-17 (Fed. Cir. 2000). Rigorous application of this requirement is the best defense against the subtle, but powerful, attraction of an obviousness analysis based on hindsight. See *Dembiczak* at 1617. Whether shown explicitly or implicitly, however, broad conclusory statements standing alone are not evidence because the showing must be clear and particular. See *id.*

Thus, it is well established that the mere fact that references can be combined does not render the resultant combination obvious unless the desirability of that combination is also taught or suggested by the prior art. See *In re Mills*, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990). Therefore, even if all elements of the claimed invention were known, this is not sufficient by itself to establish a prima facie case of obviousness without some evidence that one would have been motivated to combine those teachings as proposed by the Examiner. See *Ex parte Levengood*, 28 USPQ2d 1300, 1302 (B.P.A.I. 1993). Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 3-6 were rejected under Section 103(a) as allegedly unpatentable over Tsang et al. (U.S. Pat. Publication No. 2003/0207832) in view of Runge et al. (Biochem. Biophys. Res. Comm. 274:1-3, 2000). Applicant traverses.

Tsang et al. do not disclose transforming or transfecting the DNA construct into a human hepatocyte cell line. They only transfected human breast carcinoma and human colon carcinoma cell lines. In contrast, the claimed invention requires transformation or transfection of the DNA construct into a human hepatocyte cell line. More specifically, claims 10-17 require stable transfection of a human hepatocyte cell line. The failure of Tsang et al. to disclose the claimed invention is not remedied by the attempt in the Action to combine that disclosure with Runge et al., who mostly discuss hepatocyte primary cultures instead of hepatocyte cell lines, which are immortalized or transformed. More specifically, Runge et al. at page 2 disclose (a) infection of human hepatocytes with a retroviral expression vector and (b) a human hepatocyte cell line (NKNT-3) which was reversibly immortalized by retroviral transfer of the SV40 T antigen gene and can be differentiated by Cre/Lox mediated excision of that immortalizing gene. But it was not noted in the Action that (a) the former is a hepatocyte primary culture instead of a cell line as required by Applicant's claims and (b) no DNA construct was introduced into the latter because NKNT-3 was only used as a source for functional hepatocytes after they were induced to stop proliferating and differentiated by Cre/Lox mediated excision of the SV40 large T antigen. Review of the NCBI literature database did not indicate that any expression construct was ever introduced into such reversibly immortalized human hepatocyte cell lines. And there was no evidence provided in the Action of a reasonable expectation that (i) the DNA construct would have been successfully introduced into NKNT-3, (ii) a promoter would have been successfully inducible by heat in NKNT-3, or (iii) the protein of interest would have been successfully translated in NKNT-3 at the time Applicant's invention was made. Thus, no prima facie case of obviousness was established in the Action.

As taught in Runge et al., the major impetus for developing human hepatocyte cell lines was their use in bio-artificial liver support systems. The cited documents do not teach or suggest that it would have been desirable to replace a human cell line such as those transfected by Tsang et al. with a human hepatocyte cell line as taught by Runge et al. It is believed that Applicant was the first to teach the combination of introducing "a DNA construct in which a gene encoding a protein of interest is operably linked to a

modified heat-inducible promoter” into “a human hepatocyte cell line” for heterologous protein production. Therefore, his invention is patentable over the prior art.

Finally, Applicant submits that there would be no motivation to combine the documents because Tsang et al. do not teach or suggest the desirability of using a DNA construct containing the Hi-Hot promoter to transform or transfect a human hepatocyte cell line. Nor do Runge et al. teach or suggest introducing a DNA construct comprising a modified heat-inducible promoter into the NKNT-3 cell line. Even assuming for the sake of argument that one of ordinary skill in the art would have found it obvious to make such a combination, there was no evidence cited in the Action that there would have been a reasonable expectation of success to express a protein of interest from the Hi-Hot promoter in the NKNT-3 cell line.

The combination of Tsang et al. and Runge et al. does not render obvious the claimed invention because all limitations of independent claim 1 are not found in the cited documents. Moreover, claims depending from that independent claim are also not made obvious by the documents because the limitations of claim 1 is incorporated in the dependent claims. M.P.E.P. § 2143.03 citing *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988).

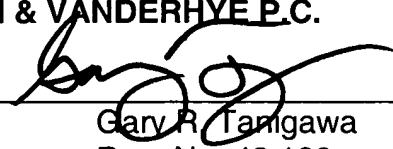
Withdrawal of the Section 103 rejection is requested because the invention as claimed would not have been obvious to one of ordinary skill in the art at the time it was made.

Applicant submits that the claims are in condition for allowance and earnestly solicit an early Notice to that effect.

Respectfully submitted,

NIXON & VANDERHYTE P.C.

By: _____


Gary R. Tanigawa
Reg. No. 43,180

901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100